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Pulmonary Edema and Pleural Effusion Produced by Acute Alpha-Naphthyl Thiourea Poisoning in Rats and Dogs. HARRISON LATTA 181

Penile Ulcer Caused by Micrococcus Tetragenus. BERNARD D. PINCK, M.D., AND BERTRAM ZHEUTLIN, M.D. 198

Proceedings of the Meetings of the Johns Hopkins Medical Society 202

Book Reviews 206

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PULMONARY EDEMA AND PLEURAL EFFUSION PRODUCED BY ACUTE ALPHA-NAPHTHYL THIOUREA POISONING IN RATS AND DOGS*

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INTRODUCTION

Previous papers showed that phenyl thiourea produces a marked pulmonary edema and pleural effusion in domestic Norway rats and kills in doses of 1 to 2 mg. per average-sized adult rat (1, 2). Later it was reported that alpha-naphthyl thiourea (subsequently referred to as ANTU) produces the same effects and has the same high toxicity; and that both ANTU and phenyl thiourea produce the same effects on recently trapped wild Norway rats (3). A combination of high toxicity and high acceptance makes ANTU an effective rodenticide. In addition, ANTU provides a means of studying the physiolgical problems of pulmonary edema and pleural effusion with relative freedom from other factors such as heart failure and pneumonia.

ANTU is toxic also to dogs, killing in doses of as small as 16 mg./kg. intraperitoneally; to mice, killing in doses as low as 50 mg./kg. intraperitoneally; and to domestic pigs, killing in doses as low as 35 mg./kg. by mouth (4, 5). It is less toxic to guinea pigs, Alexandrine rats, and cats, killing in doses of several hundred milligrams per kilogram; and practically nontoxic to rabbits and monkeys, killing only in doses of several grams per kilogram. For dogs, pigs, mice, and cats, it appears to have the same effect on the lungs as it does in the Norway rat. The other animals studied in this laboratory show little or no pulmonary edema or pleural effusion.

The present report gives a detailed account of the changes produced by ANTU poisoning in the lungs and pleural cavities of rats and dogs.

* Started under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University, and continued under a contract between the Medical Division, Chemical Corps, U. S. Army, and The Johns Hopkins University.

† Formerly of the Department of Pathology, The Johns Hopkins Medical School; now First Lieutenant, M.C., at the Army Institute of Pathology, Washington, D.C.

MATERIAL

Rats. The material consists of several sections of both lungs from each of 17 (5 males and 12 females) adult wild Norway rats, which were trapped in Baltimore in the fall of 1943. A few days after trapping (2–4 days in most instances), ANTU suspended in olive oil was injected intraperitoneally in a dosage of 33 mg./kg. Their weights varied from 256–477 gm. Three of the females were found to be pregnant and one postpartum. The rats were killed, by crushing the cervical spine, at intervals from 1 to 22 hours after injection, except for 3 rats, one of which died at 17½ hours, and the other 2 at 19½ hours. The usual survival time, after doses of this size, was 16 to 22 hours, as determined with several dozen other wild Norway rats. All of the autopsies were performed by one person. Sections were taken from the major organs and other tissues of interest. The tissues were fixed in Zenker-formalin and stained with hematoxylin and eosin. Bacterial stains were made on the lungs of the 5 longest-living rats.

Similar lung sections were prepared from 10 control wild Norway rats trapped at about the same time, and also killed by crushing the cervical vertebrae.

A few chemical and microscopic studies on bronchial and pleural fluid were made on other ANTU-treated wild Norway rats.

Ten domestic Norway albino rats were given ANTU by stomach tube (300 mg./kg. in olive oil) and killed at intervals from 30 minutes to 6 hours by fracturing the cervical vertebrae. Sections from both lungs and from the mediastinum of each animal were made.

Dogs. Fifty-three lung slides from 9 dogs, which died in 12–24 hours after receiving ANTU intraperitoneally in doses ranging from 15.7 mg./kg. to 165 mg./kg., were prepared similarly to the rat lungs. Bacterial stains were made on 3 of the lungs which showed the largest number of polymorphonuclear leukocytes.

Some of the data came from physiological observations that were made by Dr. Cecil Drinker, of the Harvard School of Public Health, on the lymph flow from the lungs and heart of one dog. Also included are the results of an experiment performed by Dr. Richard Bing, of The Johns Hopkins Hospital, on the hemodynamic effects produced by ANTU poisoning in 2 dogs.

RATS

Gross Appearance of Lungs. The striking finding at autopsy is pulmonary edema associated with pleural effusion, both of which are quite marked in the animals allowed to live a longer time after the injection of ANTU. Rats dying from ANTU poisoning are frequently found lying with their nose and mouth in the center of a large pool of fluid from the trachea. Opening the thorax discloses a remarkable sight. The pleural cavities are filled with a large amount of clear fluid which covers the lungs after having produced a partial collapse. The pleural surfaces are smooth and glistening. The lungs show an intense pulmonary edema, which has filled most of the alveoli with fluid. The entire dependent portion of the lungs—that is, the ventral half—may be completely filled with fluid so that the consistency is that of a solid jelly. On being sectioned the lungs exude a clear fluid that runs freely from the surfaces. The appearance of the cut surface varies from large areas where the air is completely replaced by fluid to other places where pink, air-containing areas are interspersed with red, fluid-containing portions. The bronchi and trachea are filled with fluid, or, in lesser degrees of pulmonary edema, they may contain a white froth. The bronchial and tracheal mucosa is pale, and the mediastinal lymph nodes are small.

Table I summarizes the observations made on 17 rats which were killed or which died at various intervals from 1 to 22 hours after poisoning. After the first hour, most of the lungs weighed more than the normal average (0.87 g. per 100 g. body weight). They showed considerable variation from rat to rat. Pleural effusion did not appear until the 2nd hour. From then on it increased somewhat irregularly until it reached a plateau after the 16th hour. A rat that died at 19½ hours showed the greatest amount of pleural effusion, 6.26 cc. per 100 g. body weight.

Microscopic Appearance of Lungs. The development of pulmonary edema can be easily traced, with individual variation, through the series of successively killed rats. The last 2 columns in Table I summarize the results. Perivascular edema appeared in both rats killed at the end of 1 hour after poisoning and alveolar edema appeared in 1 of the 2 rats killed at this time. The perivascular edema was more

marked in rats killed between 4 and 16 hours; the alveolar edema was most marked in rats which died or were killed 17 to 22 hours after poisoning. The final degree of this extraordinary edema is illustrated in Fig. 1, which is taken from a rat that died 17½ hours after the injection of ANTU. Here, the protein-containing edema fluid fills most

TABLE I

Observations on pulmonary edema and pleural effusion of wild Norway rats treated with ANTU

RAT NUMBER	SEX	KILLED OR DIED	TIME	LUNG WT. G./100 G. BODY WT.*	PLEURAL EFFUSION (CC.) PER 100 G. BODY WT.	ALVEOLAR EDEMA	PERIVASCULAR EDEMA
			hrs.				
1	F	K	1	0.74	0	0	±
2	M	K	1	1.62	0	++	+
3	M	K	2	1.13	0	+	±
4	F(pregnant)	K	2	1.34	0.10	±	++
5	F	K	4	1.17	0.42	++	+++
6	F	K	4	1.56	0.45	+	++
7	F	K	6	1.84	1.11	++	++
8	F(postpartum)	K	6	1.05	2.50	+	+++
9	F(pregnant)	K	10	0.56	2.92	++	++
10	F	K	10	1.40	3.36	++	+++
11	F(pregnant)	K	16	0.87	5.50	++	+++
12	M	K	16	1.00	0.30	+	±
13	F	D	17½	1.40	4.16	+++	+
14	M	K	18	1.17	1.80	++	+++
15	F	D	19½	1.19	6.26	+++	++
16	F	D	19½	1.84	3.80	+++	++
17	M	K	22	1.61	1.70	++	++

0 = none.
± = trace.
+ to +++ = degree of prominence.
* Average control value = 0.87 g. per 100 g. body weight.

of the alveoli in the ventral portion of the lung and even extends into the bronchi. Some of the alveolar ducts and a few of the alveoli are overdistended with air. Distention of the perivascular tissue is apparent. For contrast, a normal air-containing lung of a control rat is shown in Fig. 2.

The earliest change seen after poisoning is the distention of the perivascular lymphatics at the hilum of the lung with protein-con-

FIG. 1. PULMONARY EDEMA IN A RAT DYING FROM ANTU POISONING
Note overdistention of air-containing portions. WN13 (died at $17\frac{1}{2}$ hours) ×37.5

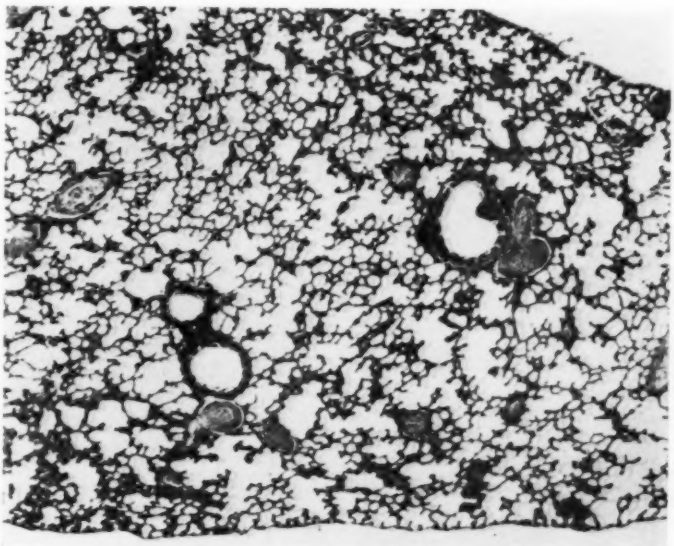

FIG. 2. LUNG FROM A CONTROL RAT FOR COMPARISON WITH FIG. 1. WN1009 ×37.5

taining fluid. Then, as the lymphatics and the perivascular tissues in both the hilum and periphery swell with fluid to a remarkable degree, fluid begins to appear in the alveoli, first lining and then filling them. Fig. 3, from a rat killed at 2 hours, shows the early distention of the

FIG. 3. DISTENDED PERIVASCULAR LYMPHATICS (L) AND TISSUES (T), WITH MOST ALVEOLI STILL AIR-CONTAINING. WN4 (KILLED AT 2 HOURS) ×25

perivascular lymphatics and tissues. With higher magnification traces of fluid are just barely visible in some alveoli in this section.

The final extreme degree of distention of the perivascular lymphatics and tissues at the hilum is demonstrated in Fig. 4, from the lung of a rat killed at 22 hours. For comparison, the corresponding area at the hilum of a control lung is shown in Fig. 5. The large hilar vessel in the lower right-hand corner of Fig. 5 corresponds to the large vessel the

FIG. 4. MARKED DISTENTION OF PERIVASCULAR LYMPHATICS AND TISSUES AT THE HILUM OF THE LUNG

Arrows mark the lymphatics. WN17 (killed at 22 hours) ×70

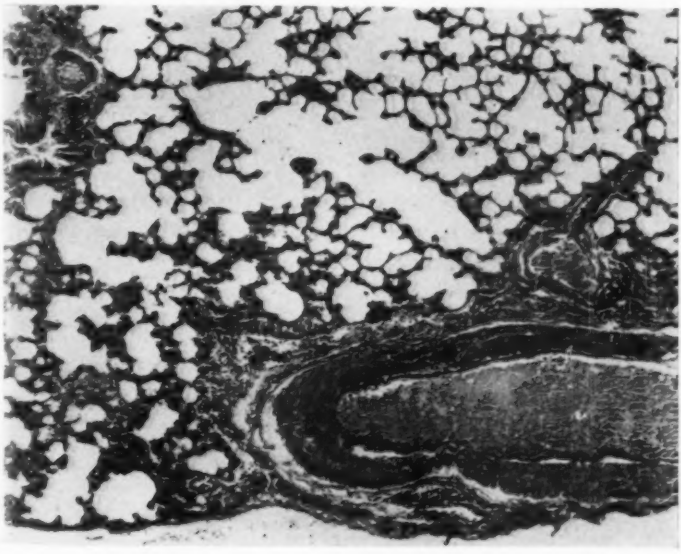

FIG. 5. A CORRESPONDING AREA AT THE HILUM OF A CONTROL LUNG FOR COMPARISON WITH FIG. 2. WN349 ×70

edge of which is seen in the upper right-hand corner of Fig. 4. Fig. 6 shows at higher magnification the edema about a medium-sized artery and vein in the periphery of the lung of a rat killed at 18 hours.

When many of the alveoli become filled with fluid, the remaining air-containing alveoli become overdistended (Fig. 1). The overdistention of a few alveoli or alveolar ducts is maintained in spite of the compression of the lung as a whole which must result from the

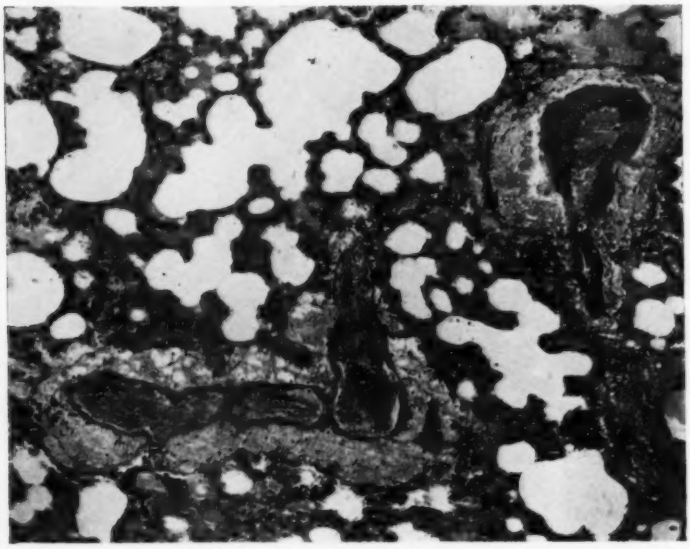

FIG. 6. EDEMA ABOUT MEDIUM-SIZED ARTERY AND VEIN IN PERIPHERY OF LUNG. WN14 (KILLED AT 18 HOURS) ×100

large pleural effusion developing along with the pulmonary edema. In many areas near the pleura in which a portion of the lung is partly filled with fluid and still partly air-containing, most, if not all, of the subpleural alveoli are filled with fluid. As might be expected, in the 3 long-living rats which died from the poisoning alone, the alveolar edema is more extensive than in the poisoned and killed animals.

The lungs of rats poisoned with ANTU do not show any definite vascular lesions, hyaline thrombi or hyaline membranes.

No correlation could be made between the state of pregnancy and the pulmonary changes. In neither of two fetal lungs were there any traces of pulmonary edema, nor did the fetal pleural cavities contain fluid. Although 3 males in this series had less pleural effusion than the corresponding females, this difference was not consistent in a few other animals. No conclusion therefore can be drawn as to sex differences.

Contents of Fluid in Lungs and Pleural Cavities. A protein-rich fluid can be seen in lymphatic channels, in the alveoli, and in the bronchi.

Many lymphocytes are found in the relatively normal lungs of control wild Norway rats, usually as localized accumulations next to a bronchus or a vessel. In the poisoned animals lymphocytes are scattered through the edematous perivascular tissues, and they are frequently seen in lymphatic channels.

In the poisoned animals a few polymorphonuclear leukocytes are seen in the alveolar fluid along with macrophages containing coal pigment. These polymorphonuclear cells are also found in the edematous perivascular tissues in varying numbers, occasionally being quite numerous. They can be found in the lymphatics much less frequently than the lymphocytes. In one of the 5 rat lungs stained for bacteria many gram-positive cocci were found. Only rare, scattered gram-positive cocci were found in the other lungs.

Erythrocytes have not been found in the edematous perivascular tissues or in the lymphatics. A few focal hemorrhages are seen in the lungs, not associated with any observed vascular or pulmonary lesion. They are interpreted as probable artifacts produced by killing or by autopsy trauma.

The pleural fluid contains protein in relatively high concentration (3.6 to 3.7 g./100 cc. in 4 wild Norway rats, whose final plasma protein concentration varied from 4.6 to 5.0 g./100 cc.). It contains enough fibrin to form a soft clot when removed from animals soon after death. The leukocytes in the pleural fluid of 5 rats varied from 360 to 1400/mm^3. Most of the cells were mononuclear, but a rare polymorphonuclear leukocyte was seen. A few erythrocytes were seen also, but the possibility of contamination in removal could not be excluded.

Mediastinal Edema. To determine the relationship between the development of pulmonary edema and mediastinal edema, 10 domestic

Norway albino rats were used. Pleural effusion first appeared at 4 hours. Microscopic sections from the lungs and mediastinum of each rat show that the edema developed more rapidly in the lung than in the mediastinum. In a rat killed at 30 minutes, when only distended lymphatics could be found in the mediastinum, the lungs showed widespread distention of the perivascular lymphatics and tissues with fluid, and an early diffuse alveolar edema. In the 2 animals killed at 6 hours there were relatively large pleural effusions with moderate alveolar edema. The perivascular tissues were quite distended and the mediastinal tissues were edematous.

Incidental Disease. It must be emphasized that the 17 wild rats used in this study came directly from the streets and cellars with their naturally occurring diseases. Six of the rats had an acute or chronic pulmonary inflammatory disease, but this did not noticeably affect the development of the edema due to ANTU. The diseased areas were localized, and the edema in the rest of the lungs was quite similar to the edema in animals with no other pulmonary disease. Nine of the animals had a helminth infestation in the liver. One had an acute pyelonephritis. Only 5 had no incidental disease in a major organ. The 10 control rats were similarly diseased.

Other Organs. Changes in organs other than the lung, particularly in the liver, adrenals, spleen and lymph nodes are observed in wild rats, but their interpretation is obscured because of the incidental diseases and the variable conditions of the wild rats' life.

DOGS

Gross Appearance of Lungs. In the dogs, the pleural effusion and pulmonary edema were usually not as marked as in the rats, probably because the dogs received relatively larger doses and so died before the effects could become as marked as in the longer-surviving rats. In this larger animal, however, perivascular edema may be easily visible in the gross, forming rings as much as 5 mm. in thickness around the medium-sized vessels.

Microscopic Appearance of Lungs. The dog lungs show a pulmonary edema of moderate to marked degree which is quite similar to that found in rats. The concentration of protein in the fluid where it only partially fills an alveolus is much greater in the dog than in the

rat. In the dog it progresses to the extent of hyaline membrane formation. In those areas of the lung which are more markedly involved, the alveoli are filled with a fluid containing a few cells, in varying proportions—macrophages, lymphocytes, and polymorphonuclear leukocytes. The few cells seen in the bronchial fluid are mostly mononuclear. The perivascular lymphatics and tissues are tremendously distended with fluid. The lymphatics of the visceral pleura are distended and there are some localized areas in which the pleural tissues are greatly edematous. This is shown in Fig. 7, which is from a dog

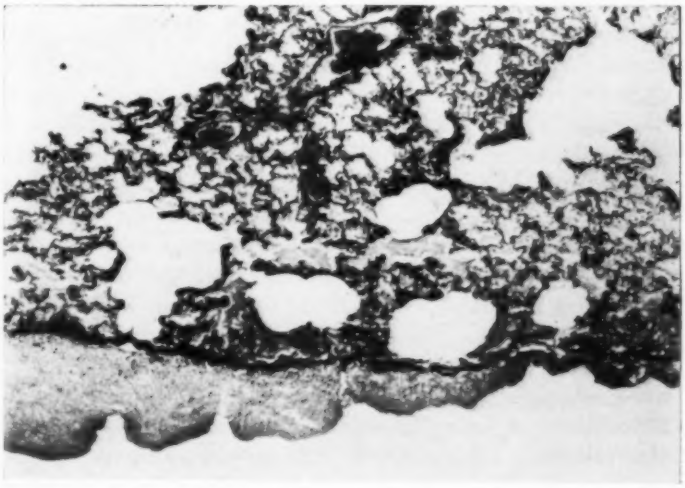

FIG. 7. EDEMA OF THE VISCERAL PLEURA. DOG 17 (DIED AT 9 HOURS) ×75

which died 9 hours after intraperitoneal injection. Another dog, killed 2½ hours after receiving ANTU, showed an early edema.

Most of the dog lungs have a few foci of acute or chronic inflammation. There are a very few hemorrhages, either associated with a focal inflammatory lesion, or with probable trauma. Such hemorrhages varied in number and size and are considered incidental to the ANTU effects. Three dogs had a moderate number of polymorphonuclear leukocytes scattered through the alveoli. Only rare gram-positive cocci were found in the bacterial stains on the three lungs. No hyaline thrombi are found in the large or small vessels.

Lymph Flow Experiment. The right lymphatic duct of a dog was cannulated by Dr. Drinker in his usual manner. The conditions and precautions necessary in this difficult technical procedure are discussed in his monograph (6, pp. 11–14). Under these conditions, with reasonably constant cardiac activity, variations in lymph flow are produced by pulmonary changes. The dog was injected intravenously with 20 mg. of ANTU per kilogram of body weight. The results are described by Dr. Drinker in his monograph (6, pp. 39–43). Because of wartime security regulations he did not state that ANTU was the thiourea derivative used.

Within the first hour after the injection of ANTU a definite increase in lymph flow was found. The amount of lymph collected increased fairly rapidly for the first 7 hours and even more rapidly thereafter. A final value of 12.6 grams of lymph per 15-minute interval was attained at the end over 8 hours later, compared to 0.4 grams before the administration of ANTU. Anoxia and the terminal increase in respiratory activity are probable factors in the terminal acceleration, but even without this the increased rate of lymph flow is remarkable. Dr. Drinker gives a vivid description of the extreme pulmonary edema and the extraordinary distention of the perivascular tissues and lymphatic-draining trunks. He concludes that as the lymphatics become unable to remove the deluge of fluid coming from the capillaries, the excess floods out into the alveoli, producing death by asphyxia.

Hemodynamic Effects. In order to evaluate the role of possible cardiac changes in the production of the pulmonary edema, the hemodynamic changes in 2 unanesthetized dogs poisoned with ANTU were observed by Dr. Bing (7).

The observations were similar in both dogs, but they were more detailed in the case of one dog. This dog was placed on the operating table, where it remained during the half hour required for each set of readings. Between observations the dog was allowed to walk around the laboratory or lie down as it desired. No food or water was given the day of the experiment. Control readings were made on the preceding night.

The cardiac output was determined by direct Fick. A catheter was introduced into the right ventricle or auricle via the external jugular vein and its position checked by fluoroscopy. Samples of arterial blood

were taken from the femoral artery, while mixed venous blood was obtained through the catheter from the right ventricle. All blood samples were taken under oil and analyzed in the Van Slyke apparatus.

The oxygen consumption was measured by means of the closed circuit method. A Blalock mask (8) was used to connect the dog's

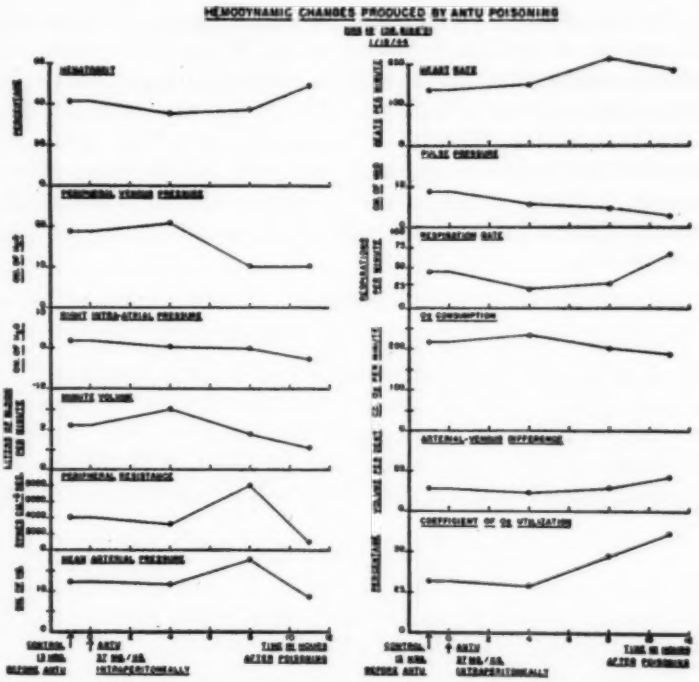

FIG. 8. HEMODYNAMIC CHANGES PRODUCED BY ANTU POISONING

head with the metabolism machine. Arterial blood pressures were optically recorded with the Hamilton manometer (9); right auricular pressures were obtained with a saline manometer. The peripheral resistance was calculated according to the formula of Apéria (10).

Observations were made before and after the injection of ANTU intraperitoneally (33 mg./kg.), and are represented graphically in

Fig. 8. Dr. Bing found a fall in peripheral venous pressure and a decrease in right intra-auricular pressure. According to him the decrease in these pressures was probably due to a decrease in circulating blood volume, as was indicated by a rise in the hematocrit (from 41.6 to 49.5), which was observed here as well as in other dogs and in rats. This animal received saline through the intracardiac catheter in order to prevent clotting in its lumen, and as a consequence the hematocrit did not rise as much as in animals which did not receive saline. It seemed possible that the decrease in venous return produced a fall in the minute volume of the heart, which at first was compensated by a rise in peripheral resistance. Towards the end of the experiment, however, the peripheral resistance and, with it, the mean arterial pressure declined. Other data are shown in Fig. 8. These cardiovascular changes seem to be due mostly, if not entirely, to fluid loss from the blood.

DISCUSSION

Pulmonary Edema. Although the evidence of pulmonary edema may develop early, being present and widespread in an hour in rats, the rats and dogs show little respiratory difficulty until 2 or 3 hours before they die, usually 12 to 24 hours later with the doses used. At death the pulmonary edema and compression by pleural fluid are extensive enough to indicate that anoxemia probably is a major factor in causing death.

From Dr. Drinker's experiment described above it seems evident that the pulmonary lymphatics become unable to drain the deluge of fluid which pours out of the alveolar capillaries and that the alveoli, bronchi, and pleural cavities fill with the excess fluid.

Dr. Bing's experimental results presented above are interpreted as indicating that the cardiovascular changes are secondary to the fluid loss in the lungs and pleural cavities. If the pulmonary edema had been caused by backward failure of the left ventricle, the right ventricular and eventually the right auricular pressures should have increased, owing to increased resistance to right ventricular output. No changes are seen microscopically in the myocardium. Furthermore, Drinker states (6, p. 44) that "increased pressure in the pulmonary capillaries does not readily cause recognizable pulmonary

edema unless coupled with heightened permeability, most frequently due to anoxia."

The edema fluid then is probably produced by an increased pulmonary capillary permeability. An interesting analogy is the striking localized edema of the head and neck of rabbits produced by paraphenylenediamine (11). Other factors and mechanisms involved in the production of pulmonary edema are discussed in a review by Henneman (12).

Pleural Effusion. Fluid is found in the pleural cavities after edema fluid appears in the lungs. This is shown in the series of 17 wild Norway rats and 10 domestic Norway rats described above.

The protein content of the pleural effusion produced by ANTU is about of the same magnitude as that of the organ lymph from dogs and other animals as listed by Drinker and Yoffey (Tables 18 and 20, 13), most of their values ranging from 2.8 to 5.3 mg. per cent. The few figures we have on rats (see above) indicate that the protein content of the pleural effusion produced by ANTU is somewhat less than that of the blood. Drinker (6) found in the dog mentioned above that the protein concentrations in the lung lymph, in the fluid from the trachea, and in the pleural fluid were identical. Another observation of his, of interest with regard to the permeability of the pulmonary capillaries, was that the lung lymph protein concentration remained almost the same before and during the entire experiment. The fibrinogen content of the pleural effusion is high enough to produce clotting, which occurs within a few minutes after the thoracic cavity is opened. In this it resembles pericardial and peritoneal fluid from normal healthy animals, which almost always clots (14). In summary, it would seem that the protein content of the pleural effusion is quantitatively similar to that of the lymph.

The figures above show that the cellular content of the effusion fluid is low, as is usual in noninfected serous fluids (15). In 2 rats (which died after 8 and 12 hours respectively) it was the same as the cell content of the bronchial fluid, within the limits of accuracy of the count (360 and 398 cells/mm^3 and 560 and 580 cells/mm^3 respectively). Polymorphonuclear cells were rarely seen among the lymphocytes and larger mononuclear cells. This corresponds with relatively normal lymph in which lymphocytes usually account for 95 per cent or more

of the cells present (13). Since some polymorphonuclear cells may be seen in the lungs of many of the animals, it may be wondered why they were not found in the effusion fluid of these two rats in larger numbers. The relatively early death of these rats may be the explanation.

CONCLUSIONS

Alpha-naphthyl thiourea produces a great increase in the permeability of the capillaries of the lungs of rats and dogs. The escaping fluid first fills the perivascular lymphatics and perivascular tissues and then later it fills the alveoli and a large part of the thoracic cavity. No other parts of the body show any edema. There is no ascites. The drug appears to have a selective effect on the capillaries in the lungs which produces a great flow of lymph from the lungs. This flow does not suffice, however, to prevent the filling of all the lung spaces and tissues. The fluid in the lungs and pleural cavities have similar protein and cellular contents, approximating the amounts present in blood serum. The capillaries show no actual damage and all of the effects are reversible. The pulmonary edema and pleural effusion, in addition to other factors, may result in death.

Acknowledgments. 1. This study was undertaken at the suggestion of Dr. C. P. Richter, who has supervised the experiments and encouraged the writer.

2. The author is indebted to Dr. A. R. Rich, who has been generous in consideration and careful in criticism of this paper.

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PENILE ULCER CAUSED BY MICROCOCCUS TETRAGENUS

BERNARD D. PINCK, M.D., AND BERTRAM ZHEUTLIN, M.D.

Since the discovery of Micrococcus tetragenus in 1881 by Koch and Gaffky, less than 200 cases of infection directly referable to this organism have been recorded. Although the paucity of reports in American literature suggests that such a disease occurs infrequently, Reimann believes that it is probably quite common, but is often disregarded or unrecognized in this country.

Micrococcus tetragenus, at first regarded as an innocuous saprophyte, was reported as a pathogenic organism in 1886 by Jakowski, and subsequent reports by Mya and Trambusti and Viquerat confirmed this finding. It is a gram-positive coccus frequently associated with other organisms in sputum, especially with the tubercle bacillus and Pfeiffer's bacillus. Smears from sputum or pus show large cocci arranged in pairs and fours, and surrounded by a broad capsule. In cultures the capsule is often absent. The colonies, which grow rather slowly, are white, are slightly smaller than those of staphylococci, and are quite viscid. The organism does not liquefy gelatin but it produces acid in glucose, lactose, saccharose, and mannite. Milk used as a culture medium becomes slightly acidified, and it usually is coagulated in from one to three days, but the coagulum is not digested.

The organism is ordinarily not virulent, and the infection follows a predisposing condition which reduces the resistance of the host and fosters the invasive quality of the organism. Sore throat, respiratory tract infection, anemia, abscesses, and urinary tract infection are reported to be the commonest predisposing factors. Micrococcus tetragenus infections have been observed also following typhoid fever, streptococcal septicemia, and brucelliasis. The infection ordinarily occurs in young adults.

The disease begins abruptly and the severity of its course is variable. There are chills, remittent fever, mild to moderate leukocytosis, and occasionally, splenomegaly. Approximately 25 fatal cases of septicemia have been recorded. The infection may become localized in various parts of the body, usually causing pneumonia, arthritis, empyema,

meningitis, and endocarditis. The occurrence of perinephric abscess has been recorded by Vease and of pyosalpinx by Wollgreen. Reimann reported prostatitis during septicemia and cultivated Micrococcus tetragenus from an urethral exudate. No previous description of genital ulcerative lesion has been discovered. A case of penile ulcer caused by Micrococcus tetragenus is reported here.

FIG. 1. PENILE ULCER CAUSED BY MICROCOCCUS TETRAGENUS

REPORT OF A CASE

The patient, a white professional soldier, aged 29, was admitted to the One Hundred and Twenty-First General Hospital on May 25, 1946 complaining of pain at the end of the penis of three days duration.

The family history was non-contributory.

The patient's past history revealed that the patient had had gonorrhea in 1943 treated with penicillin, without recurrence or reinfection. He denied syphilis by name, symptom, and treatment. There were never any complaints referable to the genitourinary system previous to the present illness, and the rest of the past history was non-contributory.

Three days prior to his admission to the hospital, the patient asserted that he fell onto the tailboard of a truck, striking his penis against a heavy chain. There was momentary pain which subsided in a few minutes. On the day of admission to the hospital the head of the penis began to swell and urination was difficult. The symptoms persisted and rapidly became more distressing; the initiation of

micturition was delayed, and obstruction seemed to be apparent at the meatus. With urination, possible only by straining, there seemed to be increasing swelling of the ventral section of the glans and frenum. On further questioning the patient admitted having practiced fellatio about twenty days before the onset of the lesion.

The physical examination revealed a well developed, well nourished white male who appeared moderately anxious about his condition. His skin, head, neck, abdomen, glandular, respiratory, and cardiovascular systems revealed no significant abnormalities. Main interest focused on the genitourinary system. There was swelling of the entire glans penis, most marked on the ventral side. At the end of the meatus was an encrusted ulceration which had no induration or discharge. There was no periurethral induration. The scrotal contents were normal. The prostate was normal in size, smooth, regular, and compressible.

Laboratory study at the time of admission showed that the red and white blood counts were within normal limits. The urine was clear, straw colored, and contained no albumin, sugar, red or white blood cells, or casts. The Kahn test was doubtful throughout the entire hospital stay with no significant change in titre, and repeated darkfield illuminations did not reveal the presence of Treponema pallidum. Culture and smears of the lesion were negative for gonococci, diptheria bacilli and the only organism grown on culture taken from the surface of the lesion was Staphylococcus albus. The intravenous pyelogram and the urine culture revealed no significant abnormalities.

Continuous soaks of various sorts were used, but no improvement was noted. The lesion increased in size and depth until on the fourteenth hospital day, it extended halfway across the glans. The eschar, which was becoming thicker and harder, was now black and had rounded, well defined edges, and the meatal lips seemed almost occluded. On the fifteenth hospital day the patient was given 16 mg. of morphine and the crust was manually broken. The lesion then revealed greater depth than was at first suspected. The entire distal portion of the glans was gangrenous. There was a foul smelling, purulent discharge and the eschar clung to the devitalized shreds of the glans. Smears and cultures were immediately taken from the purulent exudate beneath the eschar. The smear showed encapsulated gram-positive cocci in pairs and tetrads. No other organisms were seen in the smears. The anaerobic cultures produced a pure growth of organisms identified as Micrococcus tetragenus by the standards set forth above. Aerobically a few colonies of Staphylococcus albus were noted.

The sixteenth day of hospitalization the gangrenous distal portion of the glans sloughed away completely, revealing the base of the lesion covered with a milky gray, foul smelling, purulent discharge. Smears and cultures again showed a growth of organisms identified as Micrococcus tetragenus. The histologic examination of the gangrenous portion of the glans revealed large collections of leukocytes with polymorphonuclear leukocytes predominating, while the main portion of the microscopic section consisted of granulation tissue at various stages of organization. Under oil the section showed numerous organisms morphologically resembling Micrococcus tetragenus.

An indwelling catheter was inserted and therapy with zinc peroxide was begun.

Two days after the first application of zinc peroxide the lesion was washed with azochloramide and smears and cultures were taken from the base of the lesion. The cultures still showed a pure growth of Micrococcus tetragenus. Two more applications of zinc peroxide were made, each one being washed off with azochloramide after forty-eight hours. After the third and last application of zinc peroxide was removed with axochloramide, the lesion showed remarkable improvement. It had a pink base with speckled areas of gray exudate. Smears and cultures became negative after the third application of zinc peroxide. Treatment with sulfadiazine and intramuscular injection of penicillin was then begun and the indwelling catheter was retained. On the twenty-fourth hospital day, the lesion showed a clear red base with the first evidence of epithelialization from the edges.

The lesion improved uneventfully from then on, and on the thirty-sixth hospital day, after considerable epithelium had formed, the catheter was removed. Seven days later the lesion had completely healed without constriction of the meatus and the patient was discharged from the hospital. About one tenth of the glans was lost, but a three month follow up of the patient disclosed that there had been complete recovery of normal urinary and sexual function.

SUMMARY

Micrococcus tetragenus infections are probably of more common occurrence than is generally recognized. The organism is of low virulence and infection follows ordinarily a predisposing disease which reduces the resistance of the host. A case of gangrenous penile ulcer caused by Micrococcus tetragenus is reported.

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PROCEEDINGS OF THE MEETINGS OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Memorial Hall, November 11, 1946

The Strain Isolation and Serologic Studies of Influenza in Baltimore. Dr. Thomas G. Ward (Department of Medicine).

Dr. Ward's report will be published in a forthcoming issue of the Bulletin.

DISCUSSION

Dr. A. M. Fisher: It would be interesting to know how long immunity lasts in patients who have had influenza and have developed protective antibodies against the disease. I have heard that it does not last as long after a natural infection as after vaccination. I wonder if that has been confirmed or if any of the patients have been tested after six months or a year for protective antibodies.

Dr. Ward: So far as I am aware there are no adequate studies to cover Dr. Fisher's question. Dr. Francis, at Michigan, feels that individuals who have been vaccinated as long as a year are still more immune than unvaccinated persons, or at least the former group has a lower attack rate for influenza.

Hemagglutination inhibition antibodies against both influenza "A" and "B" are present in practically all adult sera, some in fairly high titer, 512 to 1024 final dilution of the sera. These seem to have no effect on prevention of the disease in man, as sera collected in the early days of disease in cases of influenza will show these antibodies.

These antibodies may be natural in occurrence or may be the result of previous exposure to "A" and "B" influenza virus.

The point is excellent and we hope to make certain observations along this line during the next epidemic.

The Etiological Problem Presented by Calcified Chest Lesions in the Presence of Negative Tuberculin Reactions. Dr. Janet Hardy (Department of Pediatrics).

Evidence has been accumulating to suggest strongly that calcified lesions seen on roentgenograms of individuals reacting negatively to relatively large doses of tuberculin may be of non-tuberculous etiology. The frequency of such calcified lesions has been demonstrated to have a very definite geographical distribution with an area of high prevalence in the Mississippi basin and the eastern slope of the Appalachian plateau.

Studies done by Christie and Peterson in Tennessee, and by Palmer on student nurses all over the United States, show a strong correlation between sensitivity to histoplasmin and calcified pulmonary lesions, suggesting that infection with histoplasma or some antigenically related organism is the etiological agent. Sayers and Merriwether suggested that Aspergillis niger is the infecting organism responsible for miliary pulmonary lesions healing with calcification. Aronson and Cox have both shown the relationship between infection with coccidioidomycosis and calcified lung lesions.

In the present study,[1] a group of 312 patients now between 15 and 30 years of age, and followed an average of 12.6 years since a primary tuberculous infection, has been retested intradermally with tuberculin and examined by roentgenograms of the chest in an effort to determine whether tuberculosis may be an etiological agent in the calcified chest lesions of negative reactors to tuberculin. It was found that of the 59 individuals having severe childhood infections, all are still hypersensitive to tuberculin a minimum of ten years after their tuberculous infection was first recognized. Of the 171 patients having mediastinal tuberculosis during childhood, only 2% fail to re[illegible] 1 milligram of tuberculin, and of the 82 patients who had a positive reaction to tuberc[illegible] but no x-ray evidence of pulmonary involvement 6% are now insensitive to 1.0 milligram of tuberculin. The rate of positive tuberculin tests in the community is not definitely known, but in a high school in a most congested area among the colored race it is only about 40%, and among the student nurses in their preclinical training, it is only about 15%. From these data it is concluded that hypersensitivity is in general retained following a primary tuberculous infection and that some other etiological agent is responsible for the high incidence of calcified chest lesions seen in tuberculin-negative individuals in the areas of high prevalence of this finding.

The Physiology of the Prostate Gland. DR. WILLIAM W. SCOTT (Department of Urology).

As an introduction to the subject, the principal methods of investigating prostatic function were enumerated, stressing particularly the information gained by a study of prostatic secretion in the dog. Illustrations were presented to show the dependence of the prostate and its secretion on androgens, castration abolishing prostatic secretion and injected androgens restoring it. Identical effects of those produced by castration were shown to be induced when estrogens were injected. Starvation effects on prostatic secretion were shown to be due to pituitary failure. A review of the known chemical constituents of the prostate gland and its secretion was presented including the important enzymes, acid phosphatase and fibrinolysin. The *in vitro* action of human prostatic slices on estrogens was discussed briefly. From these studies it was concluded that normal prostatic slices do not cause a *net* decrease or increase of the estrogenic activity of added estrogen, nor do estrogens have any effect on the rate of respiration of the slices.

DISCUSSION

Dr. J. A. C. Colston: Dr. Scott's presentation has certainly been most comprehensive and I think everyone will agree that it has brought us up to date in regard to our present knowledge of the physiology of the prostate gland. The problems which present themselves are numerous and pertain not only to the field of physiology but to chemistry and pathology and particularly to endocrinology. I am very much afraid, however, that you all would agree with me with my background—or perhaps, let us say, my lack of background—of experimental laboratory work that it would be hazardous if I should try to enter into any detailed discussion of these problems or their solution. I only hope that the rest of the members here have the satisfaction that I and the other members of the Brady staff have in the knowledge that our laboratories are reopening and I have every hope that

[1] Hardy, J. B., Persistence of Hypersensitivity to Old Tuberculins following Primary Tuberculosis in Childhood. Amer. J. of Pub. Health, **36**, 1417 (Dec. 12, 1946).

with the work that has been undertaken, some definite light will be thrown on some of these blind spots that Dr. Scott has indicated.

Dr. J. E. Howard: Dr. Scott's interesting graph showing what happens to the starving dog brings up this possibility. Supposing you found a fat fellow with a little carcinoma of the prostate, you might figure on castration at least for a few months by giving him the starvation treatment. A second thought is that you might effect that gonadal atrophy equally well by x-ray of the pituitary, because the end result would probably be the same as with castration. Lastly, what light do the physiological studies throw on a possible hormonal cause for the prostatic hypertrophy which comes on with advancing years.

Dr. Scott: In answer to Dr. Howard, may I say that it would be of great interest to see the effect of a period of starvation on prostatic cancer in a fat man. To my knowledge, pituitary irradiation has not been carried out in cases of metastatic prostatic cancer. Theoretically it should work, if androgen is responsible for the growth of tumor. I am not sure that it is. Castration may remove carcinogen; estrogen may neutralize a carcinogen. This carcinogen may not be an androgen.

With regard to benign prostatic hypertrophy, there is an effect of castration or estrogen administration on these glands. However, it is impossible in the majority of instances to wait the period of 90, 120 or 150 days to observe an effect. When a man presents himself with benign prostatic hypertrophy with acute retention of urine, it is an emergency and must be treated as such by appropriate surgical procedures. I do believe that further studies along the lines presented this evening will clarify the situation and I do believe, though I hesitate to say at this time, that some day benign prostatic hypertrophy will be a medical problem.

Dr. M. M. Ravitch: Dr. Scott, is the prostate the source of the fibrinolysin which produces the liquefaction in the blood after sudden death? If so, is this due to an agonal secretion of prostatic fluid? Would prostatectomy inhibit this activity in people or possibly animals?

Dr. Scott: Dr. Ravitch, I am unable to answer your question. It does seem clear that the source of the fibrinolysin is the prostate and not the seminal vesicles.

Dr. Evelyn Howard: I think the antagonism between estrogen and androgen is interesting and significant. There has been some difficulty in detecting such antagonism, for example in the earlier work on embryonic differentiation of the reproductive tract, but studies are beginning to make sense in this direction. I would like to ask how this fits in with the effects of estrogens on prostatic hypertrophy. Could you go into that?

Dr. Scott: Personally, I think that benign prostatic hypertropy is a tumor and not an overgrowth of the normal prostate; but there is evidence that benign prostatic hypertrophy is an overgrowth and is sensitive to androgen withdrawal. Androgen withdrawal can be accomplished by castration or its effect nullified by estrogen administration.

Guest: I would like to know if anything is known about the mechanism by which androgen and estrogen inhibit one another.

Dr. Scott: I know of no answer to that. I would like to know the answer myself and think perhaps through the study of prostatic tissue slices and slices of other secondary sex glands that we may in time learn the answer to this question; these are simply results of the experiments described, and tell us nothing of the mechanism. It is difficult for me to see from the basis of these experiments just what the mechanism is. I can not explain it through the pituitary. I think perhaps it is a direct effect but what that mechanism is I cannot say.

Dr. J. E. Howard: Well, Dr. Scott, if it is a direct effect, certain cells reflect that direct

opposition in a considerably different manner, because the ratio of antagonism as related to vaginal epithelium is quite different, in our opinion at least, from what you showed in the relative ratios in your prostatic tissues in which I know there is no direct effect. What was your ratio?

Dr. Scott: About 20 to 1.

Dr. J. E. Howard: Certainly there is no antagonistic effect of estrogen on nitrogen or potassium retention.

Dr. Scott: We do not know what the castration effect is on nitrogen retention in the patient with prostatic cancer.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal)

The Anatomy of the Bronchial Tree. By R. C. Brock. Illus. 96 pp. $12.00 *Oxford University Press, New York, New York,* 1946.

Advances in anatomy were originally largely the work of surgeons, yielded for a time to the professional anatomists, and are once more chiefly the result of the work of surgeons.

The present work, by a well-known English thoracic surgeon, is infinitely more complete—and perhaps more accurate than the treatment of the subject in any anatomy text. It is certainly more lucid and readable than some anatomical studies on the same subject by anatomists presented for surgeons. The system of bronchial nomenclature is both reasonable and simple. The book is well illustrated with x-rays, bronchograms, photographs of metal bronchial casts, colored plates of the projections of the bronchial segments, photographs of dissection, etc.

Perhaps the chief fault is that the work is done entirely from the viewpoint of the surgeon attempting to localize a lung abscess, and too little from the standpoint of the surgeon planning pulmonary resection, for whatever cause.

Nevertheless, this is an invaluable source book for those interested in the localization of pulmonary disease.

M. M. R.

The Centennial of Surgical Anaesthesia. Compiled by John F. Fulton and Madeline E. Stanton. 102 pp. $4.00. *Henry Schuman, New York, New York,* 1946.

In this year of the centennial of surgical anesthesia, the Yale historical library has published an annotated catalogue of surgical anesthesia compiled by John F. Fulton and Madeline E. Stanton. To those interested in the early history of anesthesia this bibliography will be most welcome. The short biographic sketches together with the annotations enhance the value of this brochure not a little, and possibly will extend its appeal beyond the domain of the bibliophile.

M. H. H.

The Challenge of Polio. By Roland H. Berg. 208 pp. $2.50. *The Dial Press, New York, New York,* 1946.

This small book was written primarily to inform the many people who have given dimes to the National Foundation for Infantile Paralysis, of what was being done with their money. It makes no pretense of being other than a popular account, pitched at about the level of the newspapers and digest magazines. The style,

which is the current rather breathless journalistic variety, and the continuous effort to dramatize the subject will doubtless not bother most readers but may discourage those with serious scientific interests. It is an ambitious task to critically evaluate the large amount of material represented by the research done with National Foundation support but Mr. Berg tells a story which, for the most part, is adequate. Unfortunately, the book does not seem to have any well defined plan; chapters skip from portals of entry of virus to vaccination and back to portals again. The last chapter, however, which is the best, summarizes the subject quite adequately.

There are, as might be expected, numerous inaccuracies, many of which could have been corrected by consultation with the persons whose work is quoted. For example, at one point the failure to distinguish monkeys from chimpanzees implies an inability to appreciate the large role which host differences have played in experimental work with this disease. In two other places the totally erroneous picture of monkeys "hauling themselves painfully about their cages whimpering like sick children" will doubtless give comfort to the antivivisectionists who are constantly looking for cause to attack medicine. (For the record—paralysed monkeys give no evidence of being in pain and certainly do not whimper.) But things of this sort will not prevent the non-technical readers of the book from gaining much useful information from it.

H. A. H.

Clinical Hematology. By MAXWELL M. WINTROBE. 2 Ed. Illus. 862 pp. $11.00 *Lea and Febiger, Philadelphia, Pennsylvania,* 1946.

The second edition of this excellent monograph on Hematology has been greatly modified and enlarged with the addition of many new illustrations. Recent advances in the field have been covered including the structure and use of folic acid, new data on the Rh factor and its relation to hemolytic transfusion reactions, and the effect of the nitrogen mustards on cellular mechanisms. A very worthwhile chapter on the metabolism of the erythrocyte has been added.

The author has done an excellent job of assembling the enormous amount of material in this field in a comprehensive manner while at the same time maintaining a thoroughly practical viewpoint. As a result this volume is valuable to the specialist as well as to the student and the average practitioner. Especially helpful are the cross references by page number in each chapter to related material in other sections of the book.

A. M. H.

Development Anatomy. A Textbook and Laboratory Manual of Embryology. By LESLIE BRAINERD AREY. 5th Ed. Illus. 616 pp. $7.00. *W. B. Saunders, Philadelphia, Pennsylvania,* 1946.

It would be difficult to find a more systematic, comprehensive, and lucid account of general vertebrate embryology than that offered by Arey in this latest edition of his widely known textbook. As before, the book is divided into three main sec-

tions: (1) general development, (2) special development (organogenesis), and (3) a laboratory manual for the study of chick and pig embryos. Emphasis throughout Parts I and II is placed on human embryology and strengthened by comparisons with other vertebrate groups.

Subjects treated in Part I include the origin, discharge, and union of sex cells, cleavage and gastrulation, fetal membranes of vertebrates, human embryos and their membranes, and human placentation. The new stress on human development has been made possible by the discovery and study in recent years of very early human embryos. In addition to altering the organization and content of these topics, the author now presents two entirely new and, on the whole, well-considered chapters summarizing the hormonal control of reproductive cycles and the fundamental concepts and problems of experimental embryology. The previously lengthy chapter on teratology has been drastically reduced to a few pages which, along with a short section on twinning and duplication, are now included under experimental embryology. Also discussed in this same chapter are the interpretations of early stages, the concepts of potency, embryonic induction, and gradients, and the role of genetic, hormonal, and nervous influences in vertebrate development.

Changes in Parts II and III are restricted largely to corrections and additions made necessary by discoveries during the last six years. The organogenesis of each system of the body is discussed separately and in detail. At the end of each section appears a brief comment on the anomalies which arise as a result of faulty development.

Like the preceding edition, this book is handsomely printed and well written. Its information is authoritative and its format admirably suited to both straight reading and reference work. Individual topics are easily located because the subject matter is divided into logical units, the names of structures are italicized, and the book is very well indexed. A total of 588 excellent text figures, several of them in color, make structural relationships more clear. For readers interested in pursuing certain subjects further or in following up the new and controversial interpretations discussed in the test, there is at the end of each chapter a list of references which, for the most part, cover the essential literature very adequately. All features combine to make a book which would be a valuable asset to any medical library.

F. E. W.

Disorders of the Blood. By LIONEL E. H. WHITBY and C. J. C. BRITTON. 5th Ed. Illus. 665 pp. $10.00. *The Blakiston Company, Philadelphia, Pennsylvania,* 1946.

Although there are several outstanding and exhaustive general works in hematology this is an excellent and worthy addition to them. It is clearly and concisely written.

In general the opinions offered are the most commonly accepted ones. However, the authors do not discuss in any detail and frequently do not mention contradictory

observations to certain statements they make. This is illustrated by the opinion that there is no real difference in the fragility of reticulocytes and more mature erythrocytes. Actually, there is much disagreement on this point. The statement that paroxysmal (cold) hemoglobinuria is due to a peculiar cold agglutinin is of interest for the in vitro hemolysis of this system will occur without agglutination. Furthermore, the cold agglutinin and hemolysin are apparently separate antibodies. The implication that marmite is effective in macrocytic anemias because of the extrinsic factor it contains is debatable in light of the present knowledge of "folic acid."

The only striking omissions are those of discussion of the more recent observations relative to the pathogenesis and therapy of pernicious anemia; the concepts of "hypersplenism"; anti-hemophilic fractions of plasma; and much work on iron metabolism.

The chapter on routine techniques is excellent.

The bibliographies are relatively short but quite adequate for further casual study.

Of great assistance to the reader is the careful cross index by page numbers found scattered through the text at pertinent points. This simplifies quick reference and eliminates repetition.

P. F. W.

Edinburgh Post-Graduate Lectures in Medicine. Vol. III. Published for the Honyman Gillespie Trust. 587 pp. $15.00. *Oliver and Boyd, Tweeddale Court, Edinburgh,* 1946.

In this third volume of the "Edinburgh Post-Graduate Lectures in Medicine", thirty-three lectures given under the Honyman Gillespie Trust are included. This lectureship in Scotland is somewhat comparable to the Harvey lectures in the United States. The lecturers in this group, at least, are almost entirely from Scotland, although some are from England. If there is any defect to the book at all, it is that because of the exigencies of war, it was published in 1946 despite the fact that the lectures were given in 1942 and 1943. Despite the disadvantage of this lag period, the lectures are quite up-to-date; thus, in Professor Mackie's talk on "The Problem of Air-Borne Infection", the discourse includes everything except Robertson's most recent work.

Among some of the outstanding chapters are "The Differential Diagnosis of the Chronic Affections of the Lungs", by Charles Cameron. Learmonth's essay on "Reflex Vasodilatation in Surgery", is also of interest. Other excellent chapters are those by Agnes R. MacGregor, K. Paterson Brown, A. J. C. Hamilton, and Douglas Miller. McWhirter's chapter on "The Value of Post-Operative Radiotherapy in Carcinoma of the Breast", considers the extensive experience of the Royal Infirmary in Edinburgh with 1,879 carcinomas of the breast seen in a twelve year period. The case for post-operative radiation is well supported by McWhirter's figures. In the chapter by Clayson on "Modern Trends in Preventive and Social Aspects of Tuberculosis", the interesting confession is made that just before

the war, of 1,300,000 cattle in Scotland, 650,000 were infected with the tubercle bacillus and that the control is so slow that only 6.5 per cent of the cattle have been tested as free from infection.

The lectures in this book are of the high scholastic as well as medical caliber that one would expect to come from Edinburgh. For those of us who have studied in that medical center, as well as all other medical readers, this book should have an appeal.

H. N. H.

Gynecological and Obstetrical Pathology. By EMIL NOVAK. 2nd Ed. Illus. 570 pp. $7.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1947.

The second edition of "Gynecological and Obstetrical Pathology", W. B. Saunders Co., by Emil Novak has finally made its appearance. I say "finally" because the demand for the book while out of print for the past two years has been enormous. There are several reasons for this: the excellence of the first edition; the great demand from discharged medical officers who are seeking training in gynecology; the requirement of the Obstetrical and Gynecological Specialty Board of a knowledge of pathology; and finally, the fact that the book is unique. There is no other book in the English language that covers the subject of gynecological pathology so concisely and yet so completely. The book is written from the author's own extensive experience in this branch of pathology, without attempting to give all the conflicting views on controversial subjects. This makes the book readable and clear, even to the relatively untrained. However a small bibliography is appended to each chapter for the convenience of those readers who are interested in a more comprehensive understanding of the subject.

The first chapter deals with the endocrinology of the menstrual cycle and pregnancy in a simple, concise way. In the next 28 chapters the gross and microscopic pathology of neoplastic and inflammatory diseases of the female generative tract is considered. Correlation between the pathological and clinical aspects of gynecology is in evidence throughout these chapters and, in the opinion of the reviewer, this is one of the most valuable aspects of the work. Chapters 30, 31, 32 and 33 deal with special subjects, namely ectopic pregnancy, pelvic endometriosis, implantation and placentation, and hydatidiform mole and chorioepithelioma malignum. The final chapter by L. M. Hellman deals with abnormalities and diseases of the placenta and appendages (other than hydatidiform mole and chorioepithelioma).

The new edition has expanded from 496 to 570 pages. Most of this is due to an increased number of illustrations. The first edition contained 427 pictures, whereas the second edition has 542. There was but one colored plate in the first edition and the present one contains 15. The only criticism which could be offered might be directed at the illustrations. Better sections might have been selected for the illustration of some typical lesions and more attention might have been paid to the reduction of the illustrations to the optimum size. The character of the illustrations is not quite up to that of the first edition because of the use of poorer quality paper. This is probably unavoidable due to the post-war shortage of paper.

On the whole the essential facts of obstetrical and gynecological pathology are well told and the second edition should continue to be the standard work in this field.

R. W. TEL.

Heparin in the Treatment of Thrombosis. By J. ERIK JORPES. 2nd Ed. Illus. 260 pp. $6.50. *Oxford University Press, New York, New York,* 1947.

This book by Jorpes is the second edition of his monograph first published in 1939. It is indeed a classic. The development of heparin is due primarily to three groups of men. First, Howell and McLean of Baltimore; second, Jorpes and his collaborators of the Caroline Institute in Stockholm; and third, Charles and Scott and their co-workers in Toronto. The initial work done by Jay McLean in discovering heparin as a sophomore medical student at Johns Hopkins University in 1916, should make this subject one of especial interest to all Baltimoreans.

The new edition is much more complete than the previous one. The clinical data concerning the effect of heparin is brought up-to-date, and the American Literature is given consideration as much as is the Swedish. Considering the fact that Dr. Jorpes is primarily a chemist, the clinical aspects of this book are very well presented. His discussion, for example, of the pathology of deep vein thrombosis leaves little to be desired. The illustrations in the book are excellent, and the presentation of the subject is thorough and adequate in every way. It is a book to be recommended.

H. N. H.

Journal of the History of Medicine and Allied Sciences. Vol. I. 182 pp. $2.50. *Henry Schuman, New York, New York,* 1946

With the present number, a new journal of medical history makes its debut. As the editor, Dr. George Rosen, says in the preface, its purpose is "to provide another focus for studies in medical history" (p. 4), "to cultivate medical history . . . as a vital, integral part of medicine" (ibid.), and "to present studies that can be of interest to as large a section of the medical profession as possible" (p. 5). While promising to be very broad in its scope and to maintain "the highest literary and scholarly standards" (ibid.), it will yet consider bibliographies and philological studies as more properly belonging to the *Bulletin of the History of Medicine.*

The broad scope of the journal is evidenced by the articles contained in this number. There are two contributions to *Primitive medicine* by E. H. Ackerknecht ("Incubator and Taboo") and L. C. MacKinney ("Animal Substances in Materia Medica"). *Anatomy* is dealt with by Charles Singer ("Some Galenic and Animal Sources of Vesalius") and J. B. de C. M. Saunders and C. D. O'Malley ("Bernardino Montaña de Monserrate"). Jane M. Oppenheimer ("A Note on William Blake and John Hunter") and Phyllis Allen ("Medical Education in 17th Century England") discuss chapters in the history of *English medicine,* while the articles by J. C. Trent ("The London Years of Benjamin Waterhouse") and P. I. Nixon ("Dr. Benajmin Harrison, Temporary Texan") can be assigned to the domain of *American*

medicine. The allied sciences of *pharmacy* and *dentistry* are represented by George Urdang ("Pharmacopoeias as Witnesses of World History") and Curt Proskauer ("The Two Earliest Dentistry Woodcuts"). Besides the articles, which fill the bulk of the issue, there is also a section for "Notes and Queries," edited by Max H. Fisch, and another section for "Book Reviews."

Altogether it can be said that in this first issue the Journal introduces itself as a medium for scholarly papers and in a form which is attractive by reason of its clear print, abundant illustrations and convenient format. This, together with the many well-known names constituting the Board of Editors and Consulting Editors, will assure it wide attention in this country as well as abroad.

O. T.

The Marihuana Problem. By the Mayor's Committee on Marihuana. 200 pp. $2.50. *Jacques Cattell Press, Lancaster, Pennsylvania,* 1945.

The Mayor's Committee to study the marihuana problem consisted of two internists, three psychiatrists, two pharmacologists and one public health expert, appointed by the New York Academy of Medicine. It included such well-known names as McKeen Cattell, Robert F. Loeb, Karl M. Bowman, David Wechsler and S. Bernard Wortis. They concluded that the marihuana user does not come from the hardened criminal class, and there was found no direct relationship between the commission of crimes of violence and marihuana. Smoking marihuana can be stopped abruptly with no resulting mental or physical distress comparable to that of morphine withdrawal in morphine addicts.

The clinical studies were made upon prisoners who volunteered for the study. Although some of the subjects became restless and talkative under the marihuana influence, a mental state characterized by a sense of well-being, relaxation and unawareness of surroundings, following by drowsiness, was present in most instances when the subject was left undisturbed. In company the subjects were lively and given to talkativeness, fits of laughter and good-natured joking. In a limited number of the subjects there were alterations in behavior giving rise to anti-social expression. In the total group of 77 persons studied, what are known as psychotic episodes occurred in 9 of the subjects. In the clinical study of the effect of marihuana on functions of the various organs of the body, there were found an increase in pulse rate and blood pressure and an increase in blood sugar and metabolic rate. Static equilibrium and hand steadiness were the functions most strongly affected by marihuana. In an effective dose the drug impairs intellectual functioning in general.

Mayor LaGuardia summarized his attitude as follows: "I am glad that the sociological, psychological and medical ills commonly attributed to marihuana have been found to be exaggerated insofar as the City of New York is concerned. I hasten to point out, however, that the findings are to be interpreted only as a reassuring report of progress and not as encouragement to indulgence, for I shall continue to enforce the laws prohibiting the use of marihuana until and if complete

findings may justify an amendment to existing laws. The scientific part of the research will be continued in the hope that the drug may prove to possess therapeutic value for the control of drug addiction."

This study has been subjected to severe criticism by the Journal of the American Medical Association (Editorial, 1945, vol. 127, p. 1129), especially on the basis that it gives license to the unrestricted use of marihuana. They feel that sweeping and inadequate conclusions have been drawn on a narrow and thoroughly unscientific foundation. Possibly this controversy will be of value in stimulating further study of the whole problem. While it is possible to pick flaws in the report of the committee, its findings are entitled to a good deal of consideration.

O. R. L.

A Memoir to the Academy of Sciences at Paris on a New Use of Sulphuric Ether: 1847. By W. T. G. Morton. 24 pp. $1.50. *Henry Schuman, New York, New York*, 1946.

This pamphlet should be of interest to all who have puzzled over the ether priority controversy of a hundred years ago. This is the first separate printing of the letter that was presented to the Academy by M. Arago, for Dr. Morton, in the Autumn of 1847.

H. N. H.

Quantitative Clinical Chemistry Interpretations. By John P. Peters and Donald D. Van Slyke. Vol. I. 2nd Ed. $7.00. 1041 pp. *The Williams & Wilkins Company, Baltimore, Maryland*, 1946.

The second edition of Peters' and Van Slyke's well-known work comprises a thorough revision of the text in order to bring it up to date. This is reflected by the increase in number of volumes to three, of which the first of two on "Interpretations" has been published. The principles which governed the making of the first edition in 1931 are adhered to in the present text, but, because of the tremendous bulk of information which is involved, the task of re-editing "Interpretations" has been performed by J. P. Peters while that for "Methods" has been accomplished by D. D. Van Slyke.

Otherwise, the content of the book is arranged similarly to that of the first edition and so requires little comment here. Attention should be called to the fact, not always appreciated, that "Interpretations" comprises an excellent reference text in the general field of biological chemistry. Its subject matter is extensive, the style lucid and the bibliography large. Emphasis is placed on the relation of various substances to disease, to action of drugs, and to general metabolism. In view of the fast developing prominence of physical and chemical knowledge in medical thought and the need for an extensive reorganization of medical education in keeping with it, this book can fill a much needed place at the elbow of every student of medicine, whether pre-graduate or post-graduate, whether interested primarily in clinical medicine or in some related field. While a convenient refer-

ence book, its subject matter does not permit it to be useful to someone who wishes a quick survey of some unfamiliar subject. On the other hand, it is not adequate by itself as a complete source of information for the individual who wishes to go deeply into some one field.

As a general appraisal, it may be said to fulfill its function admirably and to be of great use for persons of divergent needs. Perhaps the ideal book would approach these subjects from a more dynamic standpoint with more emphasis on both physical and organic chemistry, rather than on physiology and on substances as separate entities.

F. W. B., Jr.

A Textbook of Clinical Neurology. By J. M. Nielsen. 2nd Ed. Illus. 699 pp. $7.50. *Paul B. Hoeber, Incorporated, New York, New York,* 1946.

This textbook is clearly written and concise. It contains a wealth of information and many illustrations. The author has written chiefly from his own experience and has not merely copied the material to be found in other texts. As one might expect, since the author has written so much on the subject of aphasias and related disorders, an interesting discussion of the cortical syndromes is included.

F. R. F.

Victory over Pain. By Victor Robinson. Illus. 338 pp. $3.50. *Henry Schuman, New York, New York,* 1946.

Within the past few years there have been a number of books published on the history of anesthesia, five such appearing in 1945–46 alone. In *Victory over Pain* Dr. Robinson has presented this history in a most lucid manner in which fine diction has not served to obscure historical accuracy.

From its dark beginnings in antiquity the search of mankind for surcease from pain is traced through to the present. The text if not voluminous is certainly complete. Of particular interest is the author's mature presentation of the discovery controversy. It is made abundantly clear that the outstanding fact was that, following Morton's demonstration of anesthesia at the Massachusetts General Hospital in 1846, anesthesia came alive in the world. The role of those others who figured so tragically in the bitter altercation, Long, Wells and Jackson, is not minimized, but their accomplishments are evaluated in true perspective. As Dr. Robinson so eloquently puts it, "The four men did not meet in a tavern and pledge eternal brotherhood as the world rejoiced in the Victory over Pain. Alone they drank the wine of bitterness and tasted the lees of hatred. There was limitless glory for all, but not one would grant a share to another."

The biographic portrayals which comprise the bulk of the volume are well-drawn and charmingly delineated. It is a pleasure to see John Snow accorded the prominence he so rightly deserves for his contribution to anesthesia. Little heard of characters like Samuel Guthrie, backwoods scientist, country physician, powder-manufacturer and discoverer of chloroform; find their way into this account along

with Henry Hill Hickman who, unrecognized in his own time, understood the principles and practice of anesthesia. The subject is rounded out by a brief but adequate account of modern methods and masters.

All in all this is a thoroughly readable book. Although it will undoubtedly have wide appeal for the lay public, this should in no way detract from its appreciation by the professional man.

M. H. H.

Women in Industry: Their Health and Efficiency. By ANNA M. BAETZER. 344 pp. $4.00. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1946.

The number of women in industry has increased so rapidly in the past years that some evalutation of the effect of such numbers of women on industry and of industry on the health and lives of women so employed is urgently needed. This book reviews the available scientific facts concerning the health and efficiency of women in relation to their employment, especially material gained during the war, and it attempts to point out those phases of the problem that need further investigation. In this analysis the performance of women has been compared with that of men on similar jobs and also the specific problems of women as women have been considered.

Despite immense gains made in the utilization of women during the war there are problems still not too well handled relating to the size, weight and fatiguability of women as compared with men. The necessity of fitting the conditions of the machine to the size of the worker seems to have been incompletely recognized. While women may become fatigued more readily than men, that seems to be attributable to household cares and responsibilities and to lack of background and adaptation to industrial work rather than to any specific factor of sex. Hours of work above the recommended forty-eight hours per week were found to increase the loss of time due to sickness, absence without permission, spoiled work and accidents, according to these impressive statistics. While absenteeism is greater among women than among men, when broken down, the evidence points to more frequent but shorter absences among women, possibly indicating a tendency on the part of women to take minor illnesses more seriously than men. On the other hand women have fewer industrial accidents. This may be due to difference in exposure, since the accident rate for women is higher for non-industrial accidents (exclusive of automobile accidents) than for men. It was found, however, that the higher rate of sickness in women was due to conditions common to men and women,—i.e. respiratory and digestive diseases.

In the realm of specific gynecological conditions it seems to be more difficult to interpret the evidence of the effect of industrial work on pregnancy, on premature births, on infant mortality and on maternal deaths. The social-economic factors which enter into these problems outside industry cannot be overlooked in their evaluation in industry. There seems to be less uncertainty about the type of work that pregnant women should undertake than how late in pregnancy a wo-

men should be allowed to continue her work. "Various federal and health agencies recommend at least six weeks antepartum leave and six to eight weeks postpartum leave with seniority rating undisturbed." Dysmenorrhoea in itself seems to be a relatively unimportant factor in absenteeism though I suspect from my clinical experience that it may be an undeclared cause of sick absenteeism more often than recognized. The menopause is said to be "unimportant in industry at present" and it is clear from statistics given here that older employed women tend to have many less absences than younger women. There are complicated social-economic factors present which prevent adequate comparison of these two groups. I agree with the author, moreover, that absenteeism among women can never be correctly compared with that among men until there is equal pay and equal opportunity for advancement, as only then will maximum output and maximal cooperation of women in industry be obtained.

Among the problems still requiring investigations to which attention is directed in this study are 1) the lower fertility record of women in industry; 2) the effects of certain processes—as lifting, reaching, vibration, heavy work, for instance, in causing or aggravating diseases of the pelvic organs; 3) the extent of occupational diseases and exposure to harmful chemical substances on women employed in industry and more especially the possible increased danger to pregnant women and to fertility; 4) the incidence of "strain and stress injuries" among women and whether there is more or less susceptibility to injuries of joints—such as tenosynovitis, bursitis or arthritis—resulting from vibration, friction or trauma; 5) accident rate in relation to hours of work.

There is excellent presentation of the benefits to industry as well as to the employee from improved personnel practices and also of the important role that the industrial physician may play in the field of preventive medicine.

There are an impressive number of charts giving statistical evidence in these and many other matters. For the first time there is here amassed a body of material that should make it possible hereafter to discuss the subject of "Women in Industry" with less repetition of generally accepted views without examination of the evidence on which these views were originally based." The researcher in the field of "Woman in Industry" will be deeply indebted to Dr. Baetjer for her skillful and careful analysis of so much pertinent material.

C. McC.